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Gender and Preterm Birth: Is male fetal gender a clinically important risk factor for preterm birth in high-risk women?

Fetal gender & Preterm Birth

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Abstract

Gender differences in several adverse pregnancy outcomes have been described, including preterm labour and delivery. In the low risk population, the male fetus is at significantly higher risk of spontaneous preterm birth.

Objectives: Our objective was to examine the risk effect of fetal gender on pregnant women at higher risk of preterm birth, and therefore its potential impact on targeting management.

Study Design: This was an analysis of prospectively collected data from a dedicated inner-city Prematurity Surveillance Clinic over a sixteen-year period. All women were high-risk for preterm delivery in view of their history, which included previous late miscarriage, PTB or significant cervical surgery. Obstetric variables and pregnancy outcomes were compared in male and female babies. Demographic and risk factors were compared between groups, and both spontaneous and iatrogenic preterm delivery rates interrogated (<24, <28, <34 and <37 weeks' gestation). Risk ratios (with 95% confidence intervals) were calculated for each gestational band.

Results: In this cohort, 14.5% of women (363/2505) delivered before 37 weeks. Pregnant women were stratified by fetal gender and were comparable for referral risk factors and demographic characteristics. There was no significant association between fetal gender and incidence of miscarriage less than 24 weeks (RR 1.17, 95% CI 0.65 to 2.10, p=0.607), or preterm births 24 to 37 weeks RR 1.07 (95% CI 0.82 to 1.40, p=0.383). Furthermore, analysis by gestational band [<28 RR 0.91 (95% CI 0.60 to 1.37, p=0.647), <34 RR 1.18 (95% CI 0.89 to 1.57, p=0.257 and <37 weeks RR 1.10 (95% CI 0.91 to 1.33, p=0.309)] also showed no effect. This held true for both spontaneous and iatrogenic preterm delivery. In our high-risk cohort there was no gender difference for preeclampsia (RR 0.93, 95% CI 0.61 to 1.41, p=0.725) or preterm premature rupture of membranes (PPROM) (RR 1.14, 95% CI 0.86 to 1.50, p=0.384)

Conclusions: In a high-risk cohort there was no significant increased risk of miscarriage, spontaneous or iatrogenic PTB, preeclampsia or PPROM for the male fetus. This is contradictory to low-risk populations and confirms that gender need not be integrated into high-risk management protocols for preterm birth.

Key words: Gender, sex, preterm birth, high-risk, prediction

Introduction

Preterm birth (PTB) is a substantial pregnancy complication, causing significant morbidity and mortality. A reduction in the rates of PTB has been hampered by difficulties in risk prediction, even within a high-risk population. Gender differences in adverse pregnancy outcomes have been described, including PTB, previously. In the low risk population, the male fetus has been shown to be at increased risk of preterm delivery.[1] This has been demonstrated in Western countries (OR 1.09 to 1.24)[1,] and appears to be more significant in white compared to black populations.[2] Males have also been found to be at greater risk of preterm prelabour rupture of membranes (PPROM), at all gestations.[3] Despite this male trend, the literature suggests an increase risk of pre-eclampsia in females,[3, 4] particularly evident in extremely preterm deliveries.

Our objective was to examine the risk effect for women at high-risk of PTB, and therefore its potential impact on targeting management. We hypothesized that within our high-risk cohort, the pregnancies associated with male fetuses would be at increased risk of PTB.

Materials and Methods

This was a secondary analysis of prospectively collected outcome data from a dedicated inner-city Prematurity Surveillance Clinic (PSC) between September 2001 and 2017. All women were high-risk for preterm delivery in view of their history, which included previous late miscarriage, PTB or significant cervical surgery. Women were referred to clinic from midwives, clinicians or were self-referred. Women with multiple pregnancies were excluded from the analysis. Data was collected directly from patients or their medical notes and input into a secure online computerised database. Women with unknown or indeterminate fetal gender, or unknown pregnancy outcome were excluded.

Our outcomes were PTB less than 37 weeks (spontaneous and iatrogenic), onset of labour (spontaneous or iatrogenic), confirmed pre-eclampsia, and preterm premature rupture of membranes (PPROM). PPROM was defined as rupture of membranes more than 1 hour prior to onset of contractions, and prior to 37 weeks' gestation. Pre-eclampsia (PET) was defined as new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman. It was also diagnosed in the absence of proteinuria if accompanied by end-organ dysfunction. Other outcomes included late miscarriage, PTB less than 28 and 34 weeks (spontaneous and iatrogenic), and significant delivery details such as use of tocolytics, antibiotics, labour augmentation, prelabour rupture of membranes, maternal pyrexia, positive MSU, mode of delivery, neonatal death, and birth weight. Late miscarriage was defined as delivery between 16 weeks and 24 weeks of gestation. Patient characteristics, obstetric risk factors and short-term neonatal outcome data was collected (Table 1).

Patient characteristics and risk factors that were continuous were presented as means +/- standard deviation (SD) and were compared between groups using students T test. Categorical patient characteristics and risk factors were presented as n (%) and compared using a Chi square test. The rate of late miscarriage (16^{+0} to 23^{+6} weeks), PTB (24^{+0} to 36^{+6} weeks gestation), preterm birth <28 weeks, preterm birth <32 weeks, preterm birth <37 weeks, PPROM and PET were presented as n (%). Relative risk, Pearson's chi-square test, and 95% confidence intervals were calculated to compare these outcomes between the male and female gender groups. Similarly, secondary outcomes were presented as means +/- SD or n (%) and relative risk and chi square or t-tests were used to compare the outcomes. Analysis was performed using STATA (version 14.0); P<0.1 was taken as significant due to multiple hypothesis testing.

Results

Women were identified from an anonymous electronic database. 2516 asymptomatic high-risk women with singleton pregnancies and known fetal gender were identified who attended the Prematurity Surveillance Clinic. 11 were excluded due to unknown onset of labour. 2505 remained, of which 50.7% of women carried a male fetus (49.3% female). Overall, 14.5% (363) were delivered before 37 weeks gestation. Of those born prematurely, 63.4% (230) were spontaneous and 36.6% (133) were iatrogenic.

Patient characteristics (Table 1) and obstetric risk-factors (Table 2) were balanced between male and female sexes.

Table 3 demonstrates the delivery outcomes of the women. At each gestational category, there was no significant difference for preterm delivery between the male and female fetus (all miscarriages <24 weeks;, preterm birth, 24 to 37 weeks, and also <28 weeks, <34 weeks and <37 weeks). This held true for both spontaneous and iatrogenic deliveries. When comparing the male risk of all PTB in the black cohort (RR 0.94, CI 0.70 to 1.24, p= 0.949) and white cohort (RR 1.30, CI 0.97 to 1.76, p=0.084) there appeared to be a stronger link between the male fetus and PTB in the white cohort, however these relative risks were not statistically significant.

There was no significant difference in delivery details, such as use of tocolysis, antibiotics and augmentation between fetal genders (Table 4). The risk of PET was not significantly associated with fetal gender (RR= 0.93, 95% CI 0.61 to 1.41, p=0.725). Similarly, no differences were found in rates of PPROM (RR=1.14, 95% CI 0.86 to 1.50, p= 0.384). Finally, there was no significant difference in neonatal deaths between fetal gender, however numbers were small (n=6 female, n=8 male). As expected, there was a significant difference between the average birth weight of male and female fetuses, males were approximately 90g heavier (p=0.004).

Discussion

Our study demonstrates that there is no significant increased risk of miscarriage or PTB (spontaneous or iatrogenic) for the male fetus in women at high-risk of preterm birth based on their obstetric history. This is in contrast to current evidence in the low-risk population, which reports an increased relative risk of 1.11[5] to 1.5[6] and odds ratio of 1.4[7] for spontaneous preterm delivery in the male fetus.

The mechanism by which the male fetus predisposes to miscarriage and preterm birth in the low-risk population is unknown, with various proposed theories. It is been suggested that the placenta of the male fetus may react differently to adverse events.[8] A study reported increased infiltration of plasma cells in the basal plate, increased basal plate mononuclear lecucocytes and villitis, and increased uteroplacental chronic vasculitis within the male placenta.[9] Furthermore, lesions of chronic inflammation at the implantation site were more common in male compared to female placentas.[9] This may represent a more aggressive maternal inflammatory response to the male trophoblast, predisposing to risk of PTB.[9] Furthermore, mothers of male neonates born preterm have higher circulating pro-inflammatory cytokines, with lower anti-inflammatory IL 10 and GCSF.[4] Maternal cortisol was found to be higher from 24 to 30 weeks gestation in women carrying a male fetus, with a crossover at 30 weeks after which women carrying a female fetus has higher salivary cortisol.[10] Fetal gender may thereby affect the maternal hypothalamic-pituitary-adrenal axis and moderate fetal development and pregnancy outcome. It is thought there is a sex-specific interaction between mother, placenta and fetus which leads to differing pregnancy outcome and complications.[11]

In contrast, it has been hypothesized that increased male birth weight or antenatal complications may lead to increased iatrogenic preterm delivery, however studies have generally shown no increase in pre-labour caesarean or induction for the male fetus.[4]

With our contradictory conclusions for high-risk pregnancies, we propose that the risk affect of male gender is only evident in the absence of significant competing risk factors or pathology, such as a history of preterm birth, PPROM or cervical surgery. These significant risk factors may overwhelm the small predisposing risks differences, for example immune tolerance, between genders.

Studies have demonstrated an increased risk of early-onset preeclampsia in women carrying a female fetus, with risk equalising towards term.[3, 12] No clear mechanism has been elucidated, current theories suggest oxidative stress, inflammatory activation, immunological factors and endothelial dysfunction play a role.[3] It is suggested that the testosterone peak in the first trimester in the male fetus suppresses the inflammatory activation and oxidative stress associated with pre-eclampsia, thereby exerting a protective effect for male fetuses[3]. This is in contrast to our study, which found no significant difference between genders, despite age, body mass index, and maternal history of hypertension being balanced between the groups, however there was a trend towards significance of increased female risk of PTB in the <28 week band.

Like PET, a variety of aetiological mechanisms have been suggested as the mechanism of action for PPROM. Other studies have demonstrated an increased male/female ratio for PPROM throughout gestation.[3] PPROM involves the disruption of the membrane morphology and collagen network, and this is often related to bacterial infection or pro-inflammatory cytokines. Similarly, risk of disruption of the membrane is thought to be related to obstetric factors such as multiple pregnancy, polyhydramnios and cervical incompetence. Environmental, genetic, and behavioural factors such as smoking and substance use, which lead to increased oxidative stress have also been discussed. Recently, telomere dependent aging of the fetal membranes and microfractures within the membranes have been implicated in the aetiology of PPROM.[13] However, our study found no increased risk of PPROM for the male fetus in high-risk mothers. Other factors may supersede the gender effect on risk of PPROM.

Other studies have demonstrated the risk effect of male gender in black populations to be less significant than white[2,7] In our study our population was 31-33.5% black. However, in this study there was no statistically significant relative risk of PTB for males in either the white or black population- although we may be underpowered to demonstrate the effect of ethnicity. In addition, our population had a mean age of 32, higher than the average in the UK (30), and many other countries.[14] Our conclusions can thus only be generalizable to similar race and age populations. Further work may be required to ascertain possible gender effects on subgroups. However currently, this is the largest high-risk cohort to date, with a PTB rate of 14.5%.

Conclusion

In a high-risk multi-cultural cohort presenting to a prematurity clinic in London, there was no significant increased risk of miscarriage, spontaneous or iatrogenic PTB, preeclampsia or PPROM for the male gender fetus. This is contradictory to the current literature in low-risk populations and suggests that gender may not be useful in risk management protocols for women at high-risk of preterm birth.

Conflict of Interest

The authors have no conflict of interest to declare.

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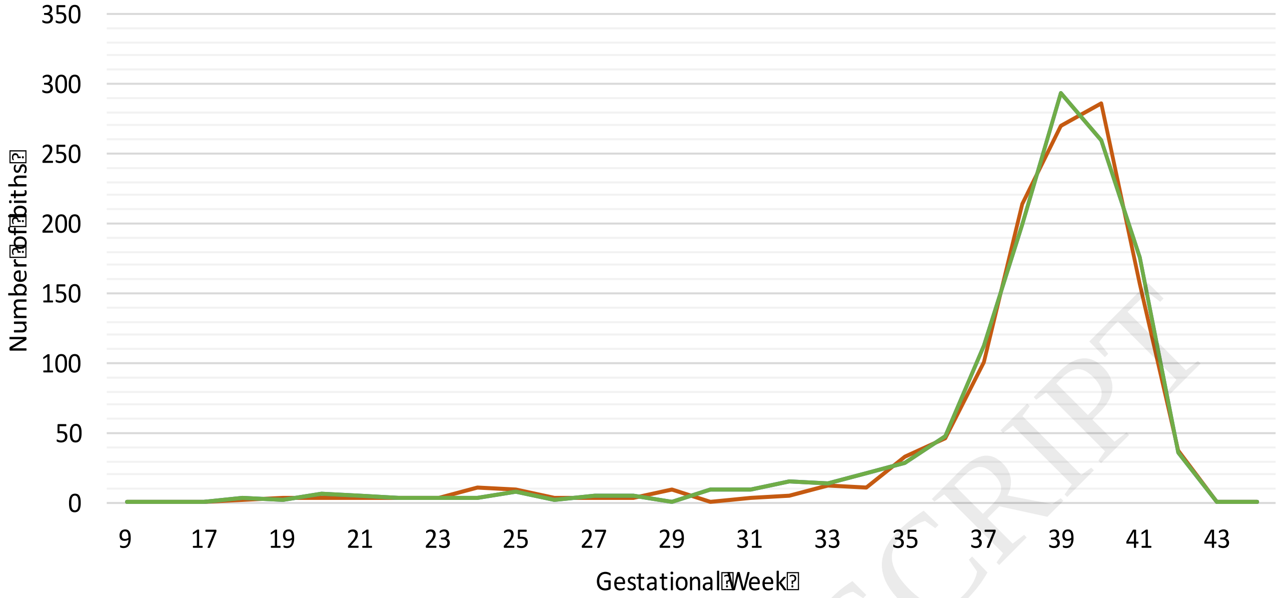

Figure 1: All deliveries by gestational week of delivery and gender in a cohort of high risk women. The red line depicts pregnancies with a female fetus and the green line, male fetus.

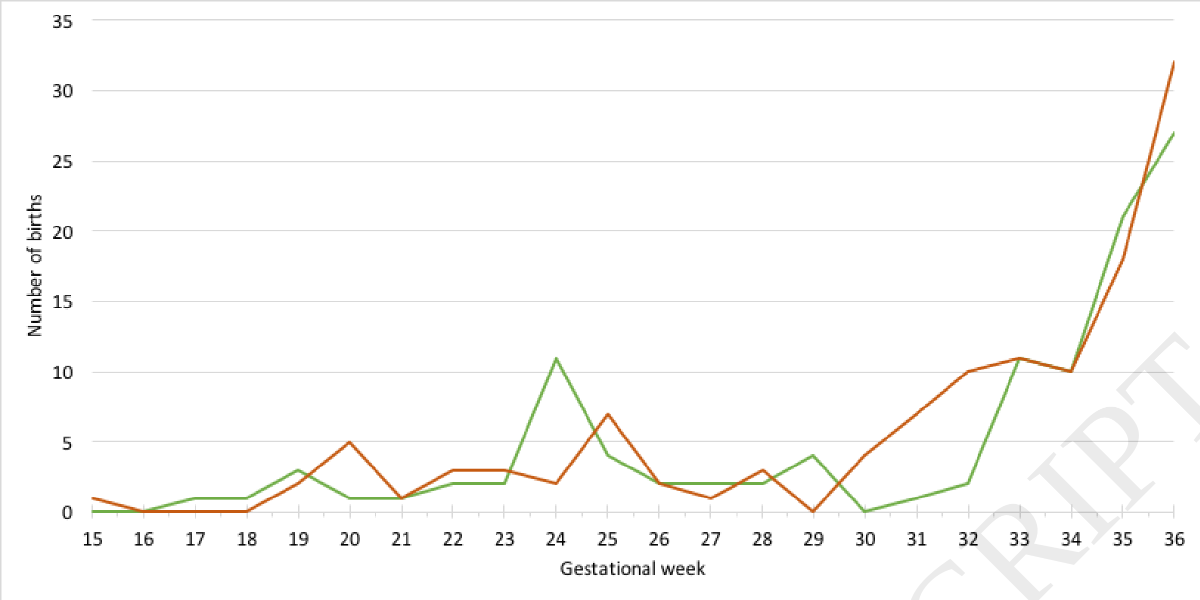

Figure 2: Spontaneous deliveries over gestational age by gender. The red line depicts spontaneous deliveries of a female fetus and the green line the spontaneous delivery of a male fetus.

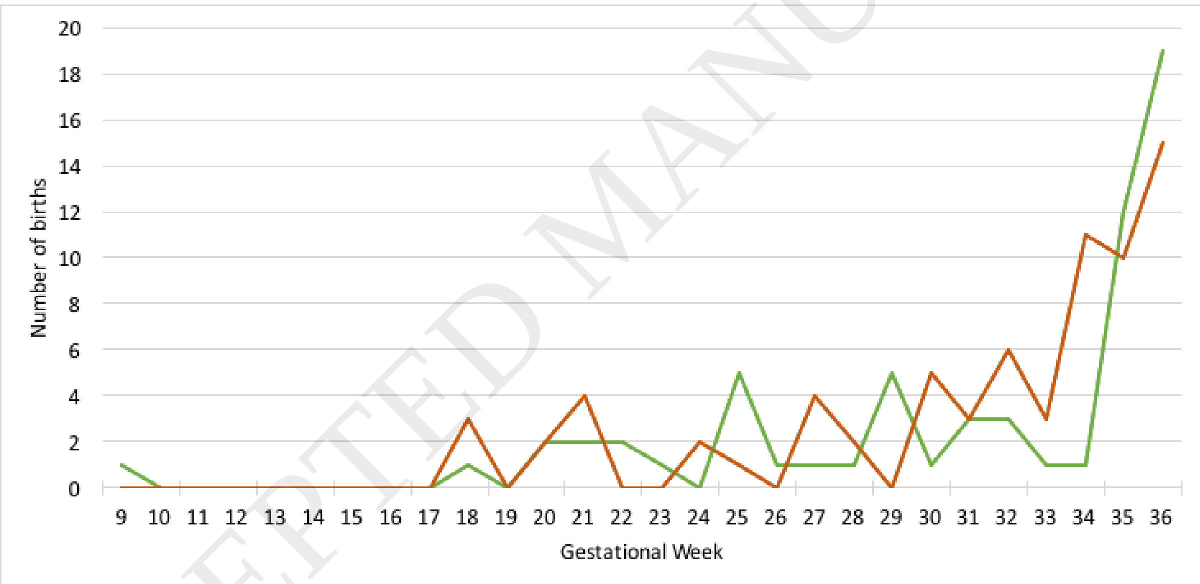

Figure 3: Iatrogenic deliveries over gestational age by gender. The red line depicts iatrogenic deliveries of a female fetus and the green line the iatrogenic delivery of a male fetus.

Table 1: Patient characteristics of 2505 pregnant women at high-risk of PTB screened at a preterm surveillance clinic

Characteristic	*Female* *n=1235 (%)*	*Male* *n=1270 (%)*
Maternal age	32.39 ± 5.5	32.04 ± 5.3
Ethnicity		
White	638 (51.7%)	686 (54.1%)
Black	414 (33.5%)	394 (31.0%)
South Asian	53 (4.3%)	45 (3.5%)
Other	129 (10.4%)	144 (11.4%)
BMI	25.6 ± 6.21	25.5 ± 5.38
Smoking		
Never smoked	926 (75.2%)	981 (77.3%)
Ex-smoker (before pregnancy)	185 (15.0%)	165 (13.0%)
Ex-smoker (in pregnancy)	55 (4.5%)	49 (3.9%)
Current smoker	66 (5.4%)	74 (5.8%)
Index of Multiple Deprivation	28.39 ± 11.03	28.10 ± 11.07

Data are given as mean ± SD or n (%).

Table 2: Obstetric risk factors of 2505 pregnant women at high-risk of PTB screened at a preterm surveillance clinic

Risk factor	*Female* *n (%)*	*Male* *n (%)*
Primigravida	294 (25.0%)	315 (26.4%)
Previous spontaneous PTB	314 (25.4%)	298 (23.5%)
Previous PPROM	138 (11.2%)	142 (11.2%)
Previous pregnancies		
Previous late miscarriage (16-23+6 weeks)	213 (17.2%)	210 (16.5%)
No. of previous pregnancies ending 14+0-23+6 weeks	0.30 (0.68)	0.29 (0.65)
No. of previous pregnancies ending 24+0 weeks or later	0.84 (1.03)	0.89 (1.12)
Past medical and surgical history		
Previous cervical surgery (e.g. LLETZ, Cone)	355 (28.7%)	388 (30.6%)
Uterine abnormality	13 (3.1%)	12 (3.0%)
Pre-existing hypertension	10 (2.3%)	6 (1.5%)
Type 2 diabetes	1 (0.2%)	2 (0.5%)
Maternal antihypertensive medication at booking	7 (1.6%)	4 (1.0%)
History of 2 or more, proven, recurrent UTIs in previous pregnancies	93 (7.5%)	73 (5.8%)
Past or present history of Domestic Violence	39 (3.6%)	53 (4.7%)

PPROM, Preterm prelabour rupture of membranes; PTB, Preterm birth; UTI, urinary tract infection

Table 3: Preterm delivery outcomes of 2505 pregnant women at high-risk of PTB screened at a preterm surveillance clinic

	Female n (%)	*Male n (%)*	*Relative Risk (95% CI)*	*P value*
All				
Miscarriage	20 (1.6%)	24(1.9%)	1.17 (0.65 to 2.10)	0.607
Delivery <28 weeks	46 (3.7%)	43 (3.4%)	0.91 (0.60 to 1.37)	0.647
Delivery <34 weeks	80 (6.5%)	97 (7.6%)	1.18 (0.89 to 1.57)	0.257
Delivery <37 weeks	170 (13.8%)	193 (15.2%)	1.10 (0.91 to 1.33)	0.309
All PTB 24 to 37 weeks	150 (12.1%)	169 (13.3%)	1.10 (0.89 to 1.35)	0.383
Spontaneous				
Spontaneous miscarriage	11 (0.9%)	15 (1.2%)	1.33 (0.61 to 2.87)	0.473
Delivery <28 weeks	30 (2.4%)	27 (2.1%)	0.88 (0.52 to 1.46)	0.611
Delivery <34 weeks	50 (4.0%)	62 (4.9%)	1.21 (0.84 to 1.74)	0.313
Delivery <37 weeks	108 (8.7%)	122 (9.6%)	1.10 (0.86 to 1.41)	0.455
All PTB 24 to 37 weeks	97 (7.9%)	107 (8.4%)	1.07 (0.82 to 1.40)	0.601
Iatrogenic				
Iatrogenic miscarriage	9 (0.7%)	9 (0.7%)	0.97 (0.39 to 2.44)	0.953
Delivery <28 weeks	16 (1.3%)	16 (1.3%)	0.97 (0.49 to 1.94)	0.937
Delivery <34 weeks	30 (2.4%)	35 (2.8%)	1.13 (0.70 to 1.84)	0.607
Delivery <37 weeks	62 (5.0%)	71 (5.6%)	1.11 (0.80 to 1.55)	0.525
All PTB 24 to 37 weeks	53 (4.3%)	62 (4.9%)	1.14 (0.80 to 1.63)	0.480
Preeclampsia with iatrogenic premature delivery	10 (0.8%)	18 (1.4%)	1.75 (0.81 to 3.78)	0.148

PTB, Preterm birth

Table 4: Other outcomes of 2505 pregnant women at high-risk of PTB screened at a preterm surveillance clinic

	Female n (%)	*Male n (%)*	*Comparison Risk Ratios (95% CI)*	*P value*
Received tocolysis?	38 (3.1%)	43 (3.4%)	1.96 (0.69 to 1.36)	0.784
Received antibiotics in pregnancy?	266 (21.7%)	278 (22.1%)	1.01 (0.87 to 1.17)	0.850
Labour augmented	185 (24.2%)	170 (21.5%)	0.89 (0.74 to 1.06)	0.197
Pre-labour ruptured membranes	32 (6.6%)	21 (4.5%)	0.68 (0.40 to 1.17)	0.165
Maternal pyrexia	35 (2.8%)	44 (3.5%)	1.22 (0.79 to 1.89)	0.368
Birthweight (g)*	3120 ± 750	3210 ± 792	89.49 (28.98 to 150.00)	0.004
Neonatal death	6 (0.5%)	8 (0.6%)	1.30 (0.45 to 3.73)	0.630
PET	44 (3.6%)	42 (3.3%)	0.93 (0.61 to 1.41)	0.725
PPROM	84 (6.9%)	98 (7.7%)	1.14 (0.86 to 1.50)	0.384

PET, pre-eclampsia; PPROM, Preterm prelabor rupture of membranes. Data are given as mean ± SD.